

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MUNRO C H ET AL: "QUALITATIVE AND SEMI-QUANTITATIVE TRACE ANALYSIS OF ACIDIC MONOAZO DYES BY SURFACE ENHANCED RESONANCE RAMAN SCATTERING" ANALYST, vol. 120, no. 4, 1 April 1995 (1995-04-01), pages 993-1003, XP000196569 the whole document	1-27
Y	EP 0 667 398 A (KYOTO DAIICHI KAGAKU KK) 16 August 1995 (1995-08-16) see whole doc. esp. claims and col.3 line 26 ff.	1-27
A	KNEIPP K ET AL: "SURFACE ENHANCED RAMAN SCATTERING (SERS) OF NUCLEIC ACIDS ADSORBED ON COLLOIDAL SILVER PARTICLES" JOURNAL OF MOLECULAR STRUCTURE, vol. 145, no. 1/02, 1 January 1986 (1986-01-01), pages 173-179, XP000196567 ISSN: 0022-2860	
A	HELMENSTINE A ET AL: "MEASUREMENT OF DNA ADDUCTS USING SURFACE-ENHANCED RAMAN SPECTROSCOPY" JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, vol. 40, 1 January 1993 (1993-01-01), pages 195-202, XP000196576 ISSN: 0098-4108	
A	MIRKIN C.A. ET AL.: "A DNA based method for rationally assembling nanoparticles into macroscopic materials" NATURE, vol. 382, - 15 August 1996 (1996-08-15) pages 607-609, XP002113276 cited in the application	
A	STORHOFF J.J. ET AL.: "One-pot colorimetric differentiation of polynucleotides with single base imperfection using gold nanoparticle probes" J. M. CHEM. SOC., vol. 120, - 11 March 1998 (1998-03-11) pages 1959-1964, XP002113277 cited in the application	
A	EP 0 838 528 A (KYOTO DAIICHI KAGAKU KK) 29 April 1998 (1998-04-29)	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01597

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 05280 A (UNIV STRATHCLYDE ; GRAHAM DUNCAN (GB); LINACRE ADRIAN MATTHEW THORN) 13 February 1997 (1997-02-13) cited in the application see whole doc. esp. claims ---	1-27
X	US 5 721 102 A (VO-DINH TUAN) 24 February 1998 (1998-02-24) cited in the application the whole document --- -/--	1,17-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

26 August 1999

Date of mailing of the international search report

07/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Müller, F

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01597

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9705280	A	13-02-1997	AU 6623896 A EP 0871774 A	26-02-1997 21-10-1998
US 5721102	A	24-02-1998	US 5814516 A US 5783389 A	29-09-1998 21-07-1998
EP 0667398	A	16-08-1995	JP 7227299 A CN 1112960 A	29-08-1995 06-12-1995
EP 0838528	A	29-04-1998	JP 10117797 A	12-05-1998

NATIONAL SEARCH REPORT

national Application No

PCT/GB 99/01597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MUNRO C H ET AL: "QUALITATIVE AND SEMI-QUANTITATIVE TRACE ANALYSIS OF ACIDIC MONOAZO DYES BY SURFACE ENHANCED RESONANCE RAMAN SCATTERING" ANALYST, vol. 120, no. 4, 1 April 1995 (1995-04-01), pages 993-1003, XP000196569 the whole document ---	1-27
Y	EP 0 667 398 A (KYOTO DAIICHI KAGAKU KK) 16 August 1995 (1995-08-16) see whole doc. esp. claims and col.3 line 26 ff. ---	1-27
A	KNEIPP K ET AL: "SURFACE ENHANCED RAMAN SCATTERING (SERS) OF NUCLEIC ACIDS ADSORBED ON COLLOIDAL SILVER PARTICLES" JOURNAL OF MOLECULAR STRUCTURE, vol. 145, no. 1/02, 1 January 1986 (1986-01-01), pages 173-179, XP000196567 ISSN: 0022-2860 ---	
A	HELMENSTINE A ET AL: "MEASUREMENT OF DNA ADDUCTS USING SURFACE-ENHANCED RAMAN SPECTROSCOPY" JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, vol. 40, 1 January 1993 (1993-01-01), pages 195-202, XP000196576 ISSN: 0098-4108 ---	
A	MIRKIN C.A. ET AL.: "A DNA based method for rationally assembling nanoparticles into macroscopic materials" NATURE, vol. 382, - 15 August 1996 (1996-08-15) pages 607-609, XP002113276 cited in the application ---	
A	STORHOFF J.J. ET AL.: "One-pot colorimetric differentiation of polynucleotides with single base imperfection using gold nanoparticle probes" J. M. CHEM. SOC., vol. 120, - 11 March 1998 (1998-03-11) pages 1959-1964, XP002113277 cited in the application ---	
A	EP 0 838 528 A (KYOTO DAIICHI KAGAKU KK) 29 April 1998 (1998-04-29) -----	

INTERNATIONAL SEARCH REPORT

ernational Application No

PCT/GB 99/01597

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 05280 A (UNIV STRATHCLYDE ;GRAHAM DUNCAN (GB); LINACRE ADRIAN MATTHEW THORN) 13 February 1997 (1997-02-13) cited in the application see whole doc. esp. claims ---	1-27
X	US 5 721 102 A (VO-DINH TUAN) 24 February 1998 (1998-02-24) cited in the application the whole document --- -/--	1,17-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 August 1999

Date of mailing of the international search report

07/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Müller, F

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01597

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9705280	A	13-02-1997	AU 6623896 A		26-02-1997
			EP 0871774 A		21-10-1998
US 5721102	A	24-02-1998	US 5814516 A		29-09-1998
			US 5783389 A		21-07-1998
EP 0667398	A	16-08-1995	JP 7227299 A		29-08-1995
			CN 1112960 A		06-12-1995
EP 0838528	A	29-04-1998	JP 10117797 A		12-05-1998

INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/GB 96/01830

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68 G01N21/65 G01N33/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A 1	US,A,5 306 403 (VO-DINH TUAN) 26 April 1994 cited in the application see the whole document ---	1,2,6-8, 21,24,25
A 2	US,A,5 266 498 (TARCHA PETER J ET AL) 30 November 1993 cited in the application see the whole document ---	1,6-8,21
A 3	JOURNAL OF RAMAN SPECTROSCOPY, vol. 14, no. 6, December 1983, CHICHESTER, pages 386-394, XP000196577 BERTOLUZZA ET AL.: "Raman and infrared spectra of spermidine" see abstract --- -/--	2,9,10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

5 November 1996

Date of mailing of the international search report

19. 11. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Ceder, 0

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/GB 96/01830

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANALYST, vol. 120, no. 4, April 1995, LONDON, pages 993-1003, XP000196569 MUNRO ET AL.: "Qualitative and semi-quantitative trace analysis of acidic monoazo dyes" cited in the application see abstract; figure 1 ---	17-19,31
A	JOURNAL OF MOLECULAR STRUCTURE, vol. 145, no. 1/2, 1986, AMSTERDAM, pages 173-179, XP000196567 KNEIPP ET AL.: "Surface enhanced raman scattering" cited in the application see abstract ---	1,7,8
A	JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, vol. 40, 1993, WASHINGTON, DC, pages 195-202, XP000196576 HELMENSTINE ET AL.: "Measurement of DNA adducts using surface-enhanced raman spectroscopy" see page 197 - page 198 ---	1
A	JOURNAL OF RAMAN SPECTROSCOPY, vol. 22, no. 12, December 1991, CHICHESTER, pages 729-742, XP000196566 COTTON ET AL.: "Application of surface-enhanced raman spectroscopy to biological systems" cited in the application -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/GB 96/01830

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5306403	26-04-94	NONE	
US-A-5266498	30-11-93	US-A- 5445972	29-08-95
		US-A- 5567628	22-10-96
		US-A- 5376556	27-12-94

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/01597

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-43 as originally filed

Claims, No.:

1-27 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1-3,18,19.

because:

PATENT COOPERATION TREATY

PCT



REC'D 17 AUG 2000

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SMK/BP5776638		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/01597	International filing date (day/month/year) 20/05/1999	Priority date (day/month/year) 20/05/1998	
International Patent Classification (IPC) or national classification and IPC C12Q1/68			
Applicant ASTRAZENECA UK LIMITED			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 02/12/1999		Date of completion of this report 11.08.2000	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Wagner, R Telephone No. +49 89 2399 7357 	

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SMK/BP5776638	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/01597	International filing date (day/month/year) 20/05/1999	(Earliest) Priority Date (day/month/year) 20/05/1998
Applicant ZENECA LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

3



as suggested by the applicant.



None of the figures.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/01597

- ☒ the said international application, or the said claims Nos. 18, as to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-3 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 19 are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-18, 20-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	4-18, 20-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	4-17, 20-27
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01597

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-3 are not clear (Article 6 PCT) because the claim includes embodiments lacking essential features (see item VIII-2).
2. Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT), which in view of the description (page 27, line 16) can be interpreted as a method of diagnosis to be carried out *in vivo*.
3. Claim 19 is not sufficiently supported by the description (Article 6 PCT) and not sufficiently disclosed (Article 5 PCT) in order to allow the skilled person to isolate a gene by using the method for detecting a target nucleic acid sequence involving SE(R)RS and colloid particles. It appears plausible that the target nucleic acid sequence is bound to the particles and could be separated by from the remaining nucleic acid sequences of the sample by removing the particles from the mixture. Nevertheless no information was given regarding the exact conditions required and especially regarding the non-specific binding of nucleic acid strands to the particles. Furthermore the isolation of genes appears to be a different invention for which Raman Spectroscopy is not required.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

1. Reference is made to the following documents:

D1: WO 97 05280 A (UNIV STRATHCLYDE ;GRAHAM DUNCAN (GB);
LINACRE ADRIAN MATTHEW THORN) 13 February 1997 (1997-02-13) cited in
the application

D2: US-A-5 721 102 (VO-DINH TUAN) 24 February 1998 (1998-02-24) cited in

the application

D3: MUNRO C H ET AL: 'QUALITATIVE AND SEMI-QUANTITATIVE TRACE ANALYSIS OF ACIDIC MONOAZO DYES BY SURFACE ENHANCED RESONANCE RAMAN SCATTERING' ANALYST, vol. 120, no. 4, 1 April 1995 (1995-04-01), pages 993-1003, XP000196569

2. Claims 1-3 are directed to a method for determining the presence or absence of a target nucleic acid sequence in a sample nucleic acid. If the lacking features (see item VIII-2) were introduced in claim 1 (it appears that the presence of at least 2 different TBS's on the surface of colloid metal particles are required to carry out the invention), the subject-matter of claims 1-3 would be identical to the subject-matter of claim 4 and hence be novel and inventive for the same reasons as those given below in section V-3.
3. The subject-matter of claim 4 and claims 5-16, if dependent on claim 4, can be considered as being novel (Article 33(2) PCT). None of the prior art documents discloses a method in which the binding of the target sequence to a target binding species (TBS) increases the surface enhancement of the SER(R)S active species (SAS) which is associated to a metal surface. In D1 (see example 1, page 57) the target sequence hybridised to the SAS-labelled TBS is separated from the remaining SAS-labelled TBS and then added to silver colloid particles. The aggregation of the silver particles is provoked and stabilised by the presence of spermine therefore the surface enhancement is not influenced by the binding of the TBS to the target sequence. The method of D2 (page 13, lines 50-54 and figure 6) detects a difference in SERS signals is caused by the hybridisation of the target to the SERS gene probe. D3 (page 1001) discloses that surface enhancement increases with the aggregation of silver colloids induced in by poly(L-lysine) without giving any indication that the colloid particles could also be aggregated by nucleic acid hybridisation. It is therefore not obvious to exploit the phenomenon of increasing the surface enhancement of Raman Spectroscopy by aggregation of the colloid particles to design a true "one pot method" for detecting a target nucleic acid sequence in a sample. Therefore the subject-matter of claim 4 and claims 5-16, if dependent on claim 4, involves an inventive step (Article 33(3) PCT).

4. For the assessment of the present claim 18 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims relating to a method of diagnosis which is to be carried out on the human body. In view of the statement in the description (page 27, line 16) that the method of diagnosis can also be carried out in vivo it appears that the method could be carried out on the human body. The methods of claims 17 and 18 should be considered as uses (see item VIII-6) of the novel and inventive method of claims 1-16 and therefore claim 17 and 18 are also new (Article 33(2) PCT) and involve an inventive step (Article 33(3) PCT).
5. The detection agents of claims 21, 22 and the process for producing them (claim 20) and the composition of claim 23 comprising two or more agents are novel (Article 33(2) PCT) because the prior art discloses detection agents always in presence of polyamines (spermine) which causes the metal particles to aggregate. The subject-matter of said claims involves an inventive step (Article 33(3) PCT) because it allows to carry out the inventive method of claims 4-16.
6. The system and apparatus of claims 24 and 25 comprising the novel and inventive agent are also novel (Article 33(2) PCT) and inventive (Article 33(3) PCT). The use of said apparatus to carry out the novel and inventive method of claims 4-16 is also new and involves an inventive step.
7. Assuming that the word "comprising" is superfluous (see VIII-9), the use of the novel and inventive method in claim 26 is also novel (Article 33(2) PCT) and involves an inventive step (Article 33(3) PCT).
8. The kit of claim 27 is new (Article 33(2) PCT). The kit of D1 (claims 26-30 and page 57 and 58) does not comprise unaggregated metal particles. The kit of the present application involves an inventive (Article 33(3) PCT) step because the presence of the unaggregated particles is essential to carry out the inventive method of claim 4.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01597

Re Item VIII

Certain observations on the international application

1. The term Target Binding Species is too vague and unclear (Article 6 PCT) and should have been defined more precisely in the claims.
2. It is clear from the description on page 15 (lines 26-31), pages 11, 12 (bridging paragraph) and page 37, line 31- page 38, line 2 that: a) the presence of 2 different TBS' on colloid particles or the presence of repetitive target sequences are required to b) aggregate the particles and to increase the surface enhancement. Since independent claim 1 and dependent claims 2 and 3 do not contain these essential features they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.
3. The expression SER(R)S active species (claims 1, 4, 8, 10, 14, 20, 21, 23) is too vague and not clear (Article 6 PCT) because it appears that even the presence or absence of hybridised nucleic acids on the metal surface gives a different signal (D2, page 13, lines 48-53) and therefore even oligonucleotides have an SER(R)S activity.
4. To clarify the meaning of the claims (Article 6 PCT) the full meaning of the abbreviations used in the independent claims (claims 1, 20, 21) should have been indicated (see also Guidelines III-4.2).
5. Claims 18 and 19 are not clear (Article 6 PCT) because they are formulated to be depending on all preceding claims and claim 17 is directed to a method which allows to phylogenetically classify an organism. Dependant claims 18 and 19 do not include all the features of claim 17 and therefore the dependency of claims 18 and 19 should have been rectified.
6. Claims 17-18 are not clear (Article 6 PCT) because they are formulated as method claims but do not disclose features of a method but the use of a method.

INTERNATIONAL PRELIMINARY

International application No. PCT/GB99/01597

EXAMINATION REPORT - SEPARATE SHEET

7. Claim 24 is not clear (Article 6 PCT) because the nucleic acid sample is not a feature of an apparatus.
8. Claim 25 is not clear (Article 6 PCT) because agents, compositions are not characterizing features of an apparatus.
9. Claim 26 is not clear (Article 6 PCT) because the word "comprising" appears to be superfluous.
10. Claim 27 is not clear (Article 6 PCT) because the formulation "one additional material" is too vague and is therefore not considered as a limiting feature.



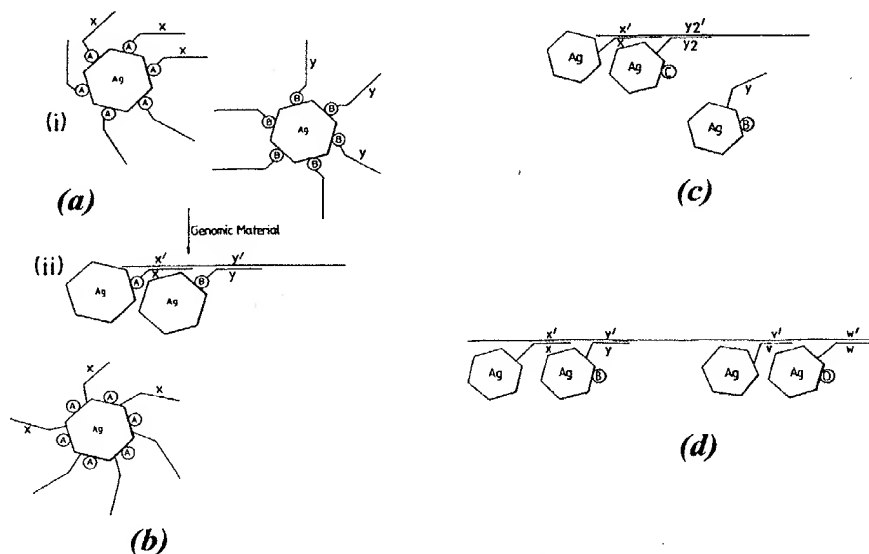
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/68		A1	(11) International Publication Number: WO 99/60157
			(43) International Publication Date: 25 November 1999 (25.11.99)
(21) International Application Number: PCT/GB99/01597		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 20 May 1999 (20.05.99)			
(30) Priority Data: 9810865.7 20 May 1998 (20.05.98) GB			
(71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): WHITCOMBE, David, Mark [GB/GB]; Zeneca Diagnostics, Research & Development Group, Gadbrook Park, Rudheath, Northwich, Cheshire CW9 7RA (GB). GRAHAM, Duncan [GB/GB]; University of Strathclyde, Dept. of Pure and Applied Chemistry, 295 Cathedral Street, Glasgow G1 1XL (GB). SMITH, William, Ewen [GB/GB]; University of Strathclyde, Dept. of Pure and Applied Chemistry, 295 Cathedral Street, Glasgow G1 1XL (GB).		Published With international search report.	
(74) Agents: KREMER, Simon, M. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).			

(54) Title: NUCLEIC ACID SEQUENCE IDENTIFICATION

(57) Abstract

Disclosed are methods for determining the presence or absence of a target nucleic acid (e.g. DNA) sequence in a sample nucleic acid, the method comprising: (a) exposing the sample to a detection agent comprising a colloid metal surface associated with a SER (R) S active species (SAS) such as an azo dye and with a target binding species (TBS) which may be PNA which is complementary to the target, (b) observing the sample/agent mixture using SER (R) S to detect any surface enhancement of the label, characterised in that the binding of the TBS to the target sequence causes surface enhancement of the



SAS. The detection agent may be exposed to the sample in step (a) as two or more separate components and will generally comprise a first agent and a second agent each having a different TBS, each TBS being capable of binding to the target sequence, and wherein the binding of the first and second TBS to the target sequence brings a metal surface associated with each TBS into proximity thereby causing surface enhancement of an SAS associated with one or both of the metal surfaces. Generally a surface seeking group such as the benzotriazole group is used to promote chemisorption of the SAS and/or TBS to the metal surface. The method may be multiplexed, and has a variety of applications, particularly in the field of molecular biology. Also provided are processes for producing detection agents, the agents themselves, and associated compositions, systems, apparatus, kits and use of the same.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

GILES, David, E.
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mersey, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year)

26 September 2000 (26.09.00)

Applicant's or agent's file reference

SMK/BP5776638

IMPORTANT NOTIFICATION

International application No.

PCT/GB99/01597

International filing date (day/month/year)

20 May 1999 (20.05.99)

1. The following indications appeared on record concerning:

☐

the applicant

☐

the inventor

☒

the agent

☐

the common representative

Name and Address

KREMER, Simon, M.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
United Kingdom

State of Nationality

State of Residence

Telephone No.

0117 926 6411

Facsimile No.

44 171 240 9339

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒

the person

☒

the name

☒

the address

☐

the nationality

☐

the residence

Name and Address

GILES, David, E.
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mersey, Alderley Park
Macclesfield, Cheshire SK10 4GR
United Kingdom

State of Nationality

State of Residence

Telephone No.

01625 514 304

Facsimile No.

01625 583 358

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the International Searching Authority

☒

the International Preliminary Examining Authority

☐

the designated Offices concerned

☒

the elected Offices concerned

☐

other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Athina Nickitas-Etienne

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

GILES, David, E.
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year)

26 September 2000 (26.09.00)

Applicant's or agent's file reference

SMK/BP5776638

International application No.

PCT/GB99/01597

IMPORTANT NOTIFICATION

International filing date (day/month/year)

20 May 1999 (20.05.99)

1. The following indications appeared on record concerning:



the applicant



the inventor



the agent



the common representative

Name and Address

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:



the person



the name



the address



the nationality



the residence

Name and Address

ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality

SE

State of Residence

SE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:



the receiving Office



the International Searching Authority



the International Preliminary Examining Authority



the designated Offices concerned



the elected Offices concerned



other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Athina Nickitas-Etienne

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

23 December 1999 (23.12.99)

International application No.

PCT/GB99/01597

Applicant's or agent's file reference

SMK/BP5776638

International filing date (day/month/year)

20 May 1999 (20.05.99)

Priority date (day/month/year)

20 May 1998 (20.05.98)

Applicant

WHITCOMBE, David, Mark et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

02 December 1999 (02.12.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38